REMARKS

Claims 22-24 and 29-40 are under examination and have been rejected. No claims have been substantively amended herein. Claim 24 has been corrected to remove "or" since these are the same antibodies.

Withdrawn Claim

Applicant gratefully acknowledges rejoinder of claim 28, which Applicant has now labeled as "original" instead of "withdrawn."

Rejection Under 35 U.S.C. 102(b)

Applicant gratefully acknowledges withdrawal of the rejection under 35 U.S.C. 102.

Rejection Under 35 U.S.C. 103(a)

Applicant gratefully acknowledges withdrawal of the previous rejection under 35 U.S.C. 103 and agreement that Johnson et al (1999) is not prior art.

Claims 22-24 and 28-40 stand rejected under 35 U.S.C. 103 as being unpatentable over Prince et al (U.S. Pat. No. 5,290,540) and Johnson et al (U.S. Pat. No. 5,824,307).

The Examiner reiterates that Prince et al (the '540 patent) teaches use of a combination of an anti-viral antibody and an anti-inflammatory agent to treat RSV but

concedes that it does not teach systemic administration of the anti-infectious agent. (See office action, page 3, bottom paragraph over to top of page 4). Instead, the Examiner now argues that Johnson et al (the '307 patent) does this.

Applicant responds that these references, either alone or in combination, fail to teach the claimed invention. Generic claim 22 is drawn to a composition comprising an anti-viral neutralizing antibody and an anti-viral agent and recites at the end of said claim "...wherein said composition is administered systemically." Thus, because the composition is administered systemically, both agents are administered systemically. Claim 31 recites administering a regimen of an anti-viral antibody and a steroid "wherein said regimen is administered systemically."

Such systemic administration of both antibody and anti-inflammatory agent is not taught by the cited patents either alone or in combination. For example, about a year after Applicants' priority date, Prince et al published the article in J. of Infect. Dis., 182, 1326-1330 (November 2000), reference K1 of Applicants' Form 1449, already submitted herein. This paper states (see page 1330, column 1, first sentence of last paragraph) that the '540 patent of Prince (listed as Reference No. 21 in that paper) was directed to <u>topical applications</u> whereas systemic use is not common and may be treated with reluctance, thereby necessitating further experimentation.

Conversely, the examples provided by Applicants in the application represent mostly systemic administration of <u>both</u> antibody and anti-inflammatory agents. For example, Applicants use triamcinolone in several of the examples of the application (describes in Figures 3 and 4).

While Prince et al (2000) is not a reference against the Applicants because most of the examples of the application were also disclosed in priority Application Serial No. 60/201,404, filed 3 May 2000 (whereas Prince et al was published electronically on 9 October 2000 - see footnote on page 1326 thereof)), it does confirm the reluctance in

the art to use systemic administration, for example, of triamcinolone. As a result, further experiments were undertaken using other anti-inflammatory agents, such as methyl prednisolone and dexamethasone (see Prince at page 1330, column 1, last 2 sentences), both of which agents were taught by Applicants in the examples of the application (see example 5, page 32, and example 6, page 34).

In addition, contrary to the Examiner's argument in support of obviousness, Applicants' methodology produced some unexpected results. Thus, Figure 4 of the Application (described at page 7, line 28, over to page 8, line 2) shows the results of antibody/steroid combination therapy on RSV pneumonia in cotton rats as described in Example 2. Panel A shows the results for virus titer for groups 1-3, panel B shows the results for virus titer for groups 4-6, and panel C shows the results for composite pathology score. These data indicate a lack of rebound pathology following systemic combination therapy. In support of this, Prince et al (2000), at page 1328, column 2, lines 5-10 (again, published after Applicants' priority date), reports that contrary to prior work rebound pathology was not a problem with the combination therapy. Thus, at the time of Applicants' priority date, those in the art would have expected such a problem to exist and Applicants were first in teaching otherwise (in their priority application).

The Examiner further argues regarding combination antibodies being motivated because multiple organisms cause respiratory disease and combination treatment would have been expected because treatment of microorganisms is known to work independently and thus should work in combination.

However, the claims are directed to systemic use of combinations of antibody and anti-inflammatory agents. If the Examiner's point is that such agents when used separately are known to be effective so that combination use should be successful, then Applicants respond that such separate use is not necessarily successful, nor is it expected to be so.

In support of this, Applicants direct the Examiner's attention to the reported ineffectiveness of systemically administered prednisolone in infant RSV (Bulow et al, Prednisolone treatment of Respiratory Syncytial Virus Infection: a randomized controlled trial of 147 infants, *Pediatrics*, 104 (6 December 1999), p e77, and cited at page 14 of the application). [attached hereto as Exhibit A with Form 1449].

The Abstract of Bulow, under the heading *Results*, states: "Prednisolone treatment had no effect on any of the outcome measures" while under *Conclusions* the last sentence states: "...corticosteroid, whether by the systemic route or by inhalation, should not be prescribed to infants with RSV infection." (emphasis added) Thus, such art (published just prior to Applicants' priority date) specifically teaches away from systemic administration of anti-inflammatory agents in treatment of RSV. Bulow is not prior art since it does not disclose combination with antibodies.

Armed with this information, at the time of Applicants' priority date, those skilled in the art would not have expected systemic administration of steroids to be useful against infectious diseases, such as RSV, while combination therapy with an antibody would be, at best, an unknown. It was thereby left to Applicants' to provide this motivation for such systemic combination methods via the present application (and its priority case).

Consequently, if the argument is that therapies known to work separately should also work in combination, Applicants respond that these therapies (systemic administration of antibody plus steroid) are not each known to work separately (per Bulow et al re steroids) and so there was no motivation to combine them.

In sum, Bulow et al (1999) teaches that steroids were not effective when administered systemically while Prince et al (2000) teaches that the Prince '540 patent (relied on to show obviousness) was directed to topical administration of steroids, that the art was reluctant to use systemic administration and that previous studies indicated

that rebound pathology (found by Applicants not to occur) was expected to result from combination therapy.

In view of the foregoing remarks, Applicants believe that the grounds of rejection have been overcome and respectfully request that the Examiner reconsider the pending claims.

Applicants have included herewith a Notice of Appeal and paid the appropriate fee for a large entity by enclosed check. If any additional fee is due, the Commissioner is authorized to charge any and all such fees to Deposit Account No. 03-0678.

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